IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 4033
Kotewicz *et al.*	Art Unit: 1652
Appl. No. 10/024,149	Examiner: *To Be Assigned*
Filed: December 21, 2001	Atty. Docket: 0942.049000A/RWE/MTT
For: **Cloned Genes Encoding Reverse Transcriptase Lacking RNase H Activity**	

Fourteenth Supplemental Information Disclosure Statement

Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants wish to bring the following information to the attention of the U.S. Patent and Trademark Office. Applicants' undersigned representative recently became aware that Clonech filed excerpts of an "Expert Statement of Joseph O. Falkinham, III," Clontech's technical expert, attached to its "Reply in Support of its Motion for Summary Judgment of Invalidity (Non-Enablement)." Because these documents are subject to a protective order ("Attorney's Eyes Only"), copies cannot be provided to the Examiner without violating a court order. Therefore, copies are not being provided for consideration by the Examiner. However, in order to complete the record as to what was contested before the District Court on the issue of enablement, Applicants provide the following information regarding Falkinham's Statement.

In contrast to Dr. Champoux's affidavit, the excerpts from Falkinham's Statement presents the following arguments:

> That Applicants' specification states that the active site of the MMLV RT RNase H was not known at the time the application was first filed and, as a result, one would have to introduce point

mutations throughout approximately 2000 nucleotides in order to obtain RNase H-deficient point mutants.

That, despite extensive experimentation over years, LTI was unable to make an RNase H-deficient mutant using smaller deletions or point mutations until the publication of Repaske *et al.* (reference AR18) and Kanaya *et al.* (reference AS17) which taught exactly what mutations should be made that affected the RNase H activity.[1]

That, while Johnson *et al.* (reference AT5) disclose conserved sequences in proteins encoded in retroviral pol genes and the *E. coli* RNase H gene, those conserved sequences are not identified as having any role in RNase H catalytic activity. In order to use the data in Johnson *et al.* to guide the choice of oligonucleotides for site-directed mutagenesis to substantially reduce RNase H activity, one would have to know what amino acids are involved in catalytic activity. That information was not provided by Johnson *et al.* or other publications at the time of filing.

That one who was aware of Johnson *et al.* would not have known where to direct site-directed mutagenesis in the region encoding the RHase H activity. Even if one were to focus only on the conserved sequences in this region, there are 5 sequences, including approximately 17 amino acids (51 nucleotides) that one could have considered changing. The LTI notebooks indicate that one single amino acid change did not produce the desired result and three mutations were required. To determine which 3 nucleotide changes should be made would require testing 132,651 combinations. Thus, Johnson *et al.* would have not enabled one to make an RNase H-deficient point mutant.

That the testimony of inventor Kotewicz indicates that the inventors had not enabled one to prepare point mutants.

That the specification does not enable one to obtain RNase H deficient mutant RTs from any virus other than MMLV. Hizi *et al.* (reference AT16) demonstrate that deletion mutations did not result in a mutant of the HIV-RT that meets the limitations of the patent

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[1]However, as pointed out in "Invitrogen Corporation's Summary Judgment Reply Brief on Enablement issues," also subject to a protective order ("Attorneys Eyes Only"), Clontech presented no evidence that Invitrogen ever attempted to prepare a point mutant until Brian Schmidt's successful preparation of one in 1990. There was a 1989 report that makes reference to a mutant that was designed to change the amino acid sequence of RT, referring to a point mutant. This document states that the mutant was to be generated in January [1990].

claims.[2] This is because, in part, HIV-RT is a dimer, a feature not contemplated by the inventors.

That LTI had difficulty in creating an RNase H-deficient RT mutant from a source other than MMLV. LTI spent years trying to obtain an RNase H-deficient mutant from RSV and AMV, and LTI had not succeeded in bringing such a product to market.[3]

That there is no teaching of an enzyme in the specification that has "substantially no RNase H activity" as defined in the specification.

That the specification does not demonstrate any mutant RT capable of improving cDNA yield, length, or any other improvement over the prior art in the generation of full length cDNA. The proposed utility of more cDNA being produced could have been the result of a mutant polymerase better able to displace viral RNA and not because of an RNase H mutation. This was not contemplated by the specification.

That his opinion is consistent with the reviewer's comments (references AR20 and AS20) who criticized the inventors' manuscript that served as a basis for drafting the specification. The reviewer had commented that 34% versus 24% yield was not a significant difference.

That in response to the reviewer's comments, the manuscript was revised to state that the enzymes were of equal efficiency. Thus, the inventors acknowledged in their published paper (reference AT6) that the enzymes in the patent did not meet the claim limitations and were not improved over the prior art.

Listed on accompanying Form PTO-1449 are documents that may be considered material to the examination of this application, in compliance with the duty of disclosure

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[2]However, as pointed out in "Invitrogen Corporation's Summary Judgment Reply Brief on Enablement issues," Hizi *et al.* describe a "carboxy-terminal deletion mutant, CT-16, that retains significant levels of polymerase activity but has no detectable RNase H activity" in HIV-RT. Hizi *et al.* at 577.

[3]Invitrogen's U.S. Appln. No. 09/064,057, filed April 22, 1998 (see document AT113), describes the preparation of RNase H deficient mutants from RSV and AMV RTs.

requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. The numbering on this Fourteenth Supplemental Information Disclosure Statement is a continuation of the numbering in Applicants' Thirteenth Information Disclosure Statement filed on herewith in connection with the above-captioned application. A copy of each document is also provided.

The Examiner's attention is directed to co-pending U.S. Patent Application Nos.:

U.S. Patent Application No. 09/064,057, filed April 22, 1998, U.S. Patent Application No. 09/245,025, filed February 5, 1999, U.S. Patent Application No. 10/292,604, filed November 13, 2002 and U.S. Patent Application No. 10/292,662, filed November 13, 2002. The specifications of US patent application Nos. 09/064,057, 09/245,025, 10/292,604 and 10/292,662 are identical, and are therefore "substantially cumulative." Accordingly, pursuant to 37 C.F.R. section 1.98(c), a single copy of this specification is submitted herewith as document **AT113**.

U.S. Patent Application No. 09/076,115, filed May 12, 1998, submitted herewith as document **AR114**;

U.S. Patent Application No. 09/220,329, filed December 24, 1998, U.S. Patent Application No. 09/220,330, filed December 24, 1998 and U.S. Patent Application No.10/024,131, filed December 21, 2001. The specifications of US patent application Nos. 09/220,329, 09/220,330 and 10/024,131 are identical, and are therefore "substantially cumulative." Accordingly, pursuant to 37 C.F.R. section 1.98(c), a single copy of this specification is submitted herewith as document **AS114**.

U.S. Patent Application No. 09/266,935, filed March 12, 1999, submitted herewith as document **AT114**;

U.S. Patent Application No. 09/533,548, filed March 23, 2000, submitted herewith as document **AR115**;

U.S. Patent Application No. 09/570,526, filed May 12, 2000, submitted herewith as document **AS115**;

U.S. Patent Application No. 09/603,613, filed June 26, 2000, and U.S. Patent Application No. 10/337,421, filed January 7, 2003. The specifications of US patent application Nos. 09/603,613 and 10/337,421 are identical, and are therefore "substantially cumulative." Accordingly, pursuant to 37 C.F.R. section 1.98(c), a single copy of this specification is submitted herewith as document **AT115**.

U.S. Patent Application No. 09/608,066, filed June 30, 2000, submitted herewith as document **AR116**;

U.S. Patent Application No. 09/697,079, filed October 27, 2000, submitted herewith as document **AS116**; and

U.S. Patent Application No. 10/224,334, filed August 21, 2002, submitted herewith as document **AT116** are directed to related technical subject matter.

The identification of these U.S. patent Applications is not to be construed as a waiver of secrecy as to these applications now or upon issuance of the present application as a patent. The Examiner is respectfully requested to consider the cited applications and the art cited therein during examination.

Where the publication date of a listed document does not provide a month of publication, the year of publication of the listed document is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the month of publication is not in issue. Applicants have listed publication dates on the attached PTO-1449 based on

information presently available to the undersigned. However, the listed publication dates should not be construed as an admission that the information was actually published on the date indicated.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered. This statement should not be construed as a representation that a search has been made, or that information more material to the examination of the present patent application does not exist.

This Fourteenth Supplemental Information Disclosure Statement is being filed before the mailing date of a first Office Action on the merits. Thus, no statement or fee is required.

Consideration of the cited documents and making the same of record in the prosecution of the above-identified application is respectfully requested. The U.S. Patent and

Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

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FORM PTO-1449 FOURTEENTH SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT	ATTY. DOCKET NO. 0942.049000A/RWE/MTT	APPLICATION NO. 10/024,149
	APPLICANT Kotewicz *et al.*	
	FILING DATE December 21, 2001	GROUP 1652

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB-CLASS	FILING DATE
	AA						
	AB						
	AC						
	AD						
	AE						
	AF						
	AG						
	AH1	6,140,086	10/31/2000	Fox *et al.*			08/14/1998
	AI1	2002/0028447 A1	03/07/2002	Li *et al.*			02/29/2000
	AJ1	6,399,334 B1	06/04/2002	Li *et al.*			09/23/1998
	AK1	6,518,019	02/11/2003	Gerard *et al.*			02/05/1999

FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB-CLASS	TRANSLATION
	AL						Yes No
	AM1	WO 98/47912 A1	10/29/1998	WIPO			Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR		
	AS	112	Hizi, A. *et al.*, "Effects of Small Insertions on the RNA-Dependent DNA Polymerase Activity of HIV-1 Reverse Transcriptase," *Virol.* *170*:326-329, Academic Press, Inc. (1989).
	AT	112	Hizi, A. *et al.*, "Mutational Analysis of the DNA Polymerase and Ribonuclease H Activities of Human Immunodeficiency Virus Type 2 Reverse Transcriptase Expressed in *Escherichia coli*," *Virol.* *180*:339-346, Academic Press, Inc. (1991).

EXAMINER	DATE CONSIDERED

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

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	AA2	2002/0177155 A1	11/28/2002	Li *et al.*			05/13/2002
	AB2	6,495,350 B1	12/17/2002	Lee *et al.*			12/23/1999
	AC						
	AD						
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	AK						

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	AL						Yes No
	AM						Yes No
	AN						Yes No
	AO						Yes No
	AP						Yes No

OTHER (Including Author, Title, Date, Pertinent Pages, etc.)

	AR	113	Hostomsky, Z., *et al.*, "Reconsitution *in vitro* of RNase H activity by using purified N-terminal and C-terminal domains of human immunodeficiency virus type 1 reverse transcriptase," *Proc. Natl. Acad. Sci. USA 88*:1148-1152, National Academy of Sciences (1991).
	AS	113	Declaration of James J. Champoux with Exhibits 1-11 attached, filed December 16, 2002 in parent U.S. Patent Application No. 09/220,330.
	AT	113	Pending United States Patent Application Nos. 09/064,057, 09/245,025, 10/292,604 and 10/292,662, Gerard *et al.*, filed April 22, 1998, February 5, 1999, November 13, 2002 and November 13, 2002 respectively.

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	AR	114	Pending United States Patent Application No. 09/076,115, Gruber *et al.*, filed May 12, 1998.
	AS	114	Pending United States Patent Application Nos. 09/220,329, 09/220,330 and 10/024,131, Kotewicz *et al.*, filed December 24, 1998, December 24, 1998 and December 21, 2001 respectively.
	AT	114	Pending United States Patent Application No. 09/266,935, Li *et al.*, filed March 12, 1999.

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	AR	115	Pending United States Patent Application No. 09/533,548, Hughes, A. John R., filed March 23, 2000.
	AS	115	Pending United States Patent Application No. 09/570,526, Astatke *et al.*, filed May 12, 2000.
	AT	115	Pending United States Patent Application Nos. 09/603,613 and 10/337,421, Lin *et al.*, filed June 26, 2000 and January 7, 2003 respectively.

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	AR	116	Pending United States Patent Application No. 09/608,066, Astatke *et al.*, filed June 30, 2000.
	AS	116	Pending United States Patent Application No. 09/697,097, Fox *et al.*, filed October 27, 2000.
	AT	116	Pending United States Patent Application No. 10/224,334, Lee *et al.*, filed August 21, 2002.

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